Predictors of poor neurologic outcome after induced mild hypothermia following cardiac arrest

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E. Al Thenayan, MD
M. Savard, MD
M. Sharpe, MD
L. Norton, BSc
B. Young, MD

Address correspondence and reprint requests to Dr. G. Bryan Young, Department of Clinical Neurological Sciences, London Health Sciences Centre-University Hospital, 339 Windermere Rd., London, Ontario, Canada N6A5A5

ABSTRACT

Background: Several predictors of poor neurologic outcome after cardiac arrest (CA) were proven to be valid. However, these studies preceded the advent of therapeutic induced mild hypothermia (TIMH), which may alter their validity. The objective of this study is to reassess the validity of these predictors in post-CA patients treated with TIMH.

Methods: Retrospective chart review of 37 consecutive adults who were comatose after resuscitation from CA and treated with TIMH.

Results: None of six patients without pupillary reactivity, six without corneal reflexes on day 3, or eight with myoclonus status epilepticus recovered awareness. Two of 14 patients with motor responses no better than extension at day 3 recovered motor responses only after 6 days post-arrest (one at 5 and one at 6 days post-rewarming) and regained awareness.

Conclusions: Loss of motor responses better than extension on day 3 was not prognostically reliable after therapeutic induced mild hypothermia for comatose cardiac arrest survivors. None of the patients who lost pupillary or corneal reflexes on day 3 or developed myoclonus status epilepticus recovered awareness. ***Neurology***® **2008;71:1535–1537**

GLOSSARY

AAN = American Academy of Neurology; **CA** = cardiac arrest; **FPR** = false-positive rate; **SSEP** = somatosensory evoked potential; **TIMH** = therapeutic induced mild hypothermia.

Accurate prediction of the neurologic outcome of comatose patients following cardiac arrest (CA) is essential in deciding on the level of care, including end-of-life decisions. To better define prognostic indicators of a poor neurologic outcome following CA, a practice parameter was established by the American Academy of Neurology (AAN).[1] The report recommended the following prognostic indicators of poor neurologic outcome for these patients: the presence of myoclonus status epilepticus, absent pupillary and corneal reflexes and motor responses no better than extension on day 3, bilaterally absent N20 responses of somatosensory evoked potentials on days 1 to 3, and elevated serum neuron-specific enolase >33 g/L at days 1 to 3 after CA.

The AAN guidelines were based on studies that preceded the "hypothermic protocol" for comatose survivors of cardiac arrest; a 12- to 24-hour period of therapeutically induced mild hypothermia (TIMH, 32–34°C) is the standard of care for comatose patients with CA who meet entrance criteria, following its demonstrated beneficial effect on both mortality and morbidity.[2,3]

We wondered if these established predictors of neurologic outcome in comatose survivors of cardiac arrest would be confounded by the protective effects of mild hypothermia and/or by sedative and paralytic agents used during the hypothermia protocols. We therefore reviewed

From the Departments of Clinical Neurological Sciences (E.A.T., M.S., B.Y.) and Anesthesia and Perioperative Medicine (M.S., L.N.), Program in Critical Care, University of Western Ontario, London, Canada; Department of Medicine (E.A.T.), King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia; and Department of Neurosciences (M.S.), Hôpital de l'Enfant-Jésus du CHA, Laval University, Quebec City, Quebec, Canada.

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our cardiac arrest cases treated with hypothermia to determine if these AAN guidelines were still valid in predicting poor neurologic outcome.

METHODS With approval from our institutional Research Ethics Board for Health Sciences Research Involving Human Subjects, a retrospective chart review was conducted on all adult CA survivors admitted to the Medical and Surgical Intensive Care Unit, the Critical Care and Trauma Centre, and the Cardiac Surgery Recovery Unit at the London Health Sciences Centre between January 2003 and February 2007.

Our inclusion criteria included adult patients (age >17 years) in coma (Glasgow Coma Scale score <9) following CA who received TMIH. Patients were excluded if they were brain dead or died within the 3-day period after CA. The following data were collected: pupillary and corneal reflexes and motor responses from day 3 to day 6, the presence of myoclonus status epilepticus, and whether the patient recovered awareness prior to hospital discharge (demonstrated by documentation of the ability of the patient to obey simple commands) and Glasgow Outcome Scale on survivors at 3 months. The false-positive rate (FPR) and 95% CIs were calculated for each of the predictors according to the formula 1 − specificity.

A preprinted protocol for TIMH was used for all comatose survivors of CA. It included specific inclusion and exclusion criteria, methods of sedation, paralysis, and cooling. Continuous infusions of midazolam, fentanyl, and cisatracurium (a muscle relaxant with very short half-life) were used during the 24-hour period of hypothermia and discontinued once the patient reached a core temperature of 36°C. The dose of cisatracurium was titrated according to the muscle response of bedside stimulator ("train of four" response). Care was taken that muscle response to stimulation was present in all patients immediately following discontinuation of hypothermia.

RESULTS A total of 282 charts of patients with the diagnosis of CA were identified and screened. Thirty-seven patients fulfilled our criteria. None of the six patients without pupillary reactivity on day 3 recovered awareness with a FPR of 0% (95% CI: 0–0.48). One of the patients was blind prior to CA and therefore was not included in the analysis. None of the six patients with absent corneal reflexes recovered awareness with a FPR of 0% (95% CI: 0–0.48). Two of 14 patients with motor responses no better than extension at day 3 regained awareness, defined as obeying commands and interacting with their environment, giving a FPR of 14% (95% CI: 0. 03–0.44). The responses were consistently documented to be absent before day 6 after CA. One of these patients died during the same admission due to a non-neurologic cause and the other patient left the hospital with a mild disability with a Glasgow Outcome Score of four on a 3-month follow-up. Two other investigators who confirmed the abovementioned findings subsequently reviewed charts of these patients. All eight patients with myoclonus status epilepticus did not recover awareness with FPR of 0% (95% CI: 0–0.4).

DISCUSSION Although the AAN recommendations are very helpful in determining prognosis that are used to make end of life decisions for comatose survivors of CA, they were based on studies that preceded the advent of therapeutic hypothermia following CA. Since TIMH is increasingly being incorporated into clinical practice (in our center more than 60% of comatose CA survivors received TIMH and this proportion is increasing), these indicators needed to be re-evaluated in this population. Our study demonstrated that the absence of motor responses better than extensor posturing on day 3 is not a sufficiently reliable predictor of poor neurologic outcome. The other predictors correlated well with the AAN recommendations.

There are several limitations of this study: 1) the sample size is small and may not be truly reflective of this patient population; 2) the data collection was retrospective; 3) we did not include somatosensory evoked potential (SSEP) testing in our center, due to its inconsistent availability in our center. The absence of the N20 response with median nerve SSEP testing has been shown to be the most reliable predictor of poor neurologic outcome after cardiac arrest.[1] Like other predictors, SSEPs warrant testing in CA patients treated with TIMH. Although this should be formally addressed, it seems likely that the absence of the response from the primary somatosensory cortex will continue to be a reliable indicator of poor outcome, as it is so robust. A study by Kottenberg-Assenmacher and colleagues showed that the N20 response was preserved even with a mean arterial blood pressure of 40 mm Hg and a temperature of 32°C.[4] Although neuron-specific enolase testing was not available in our center, it appears to be highly predictive; it should also be tested in patients treated with hypothermia to determine its FPR and the optimal timing for its determination.[1,5]

Nonetheless, our preliminary study suggests that the absence of motor response before day 6 from the time of the CA needs to be interpreted with caution. While we suggest further study to reconfirm the validity of prognostic indicators that were developed prior to the advent of hypothermia therapy, our results suggest that the clinical parameters other than motor response are valid.

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